BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Appellant(s): Blue, Jeffrey T.

Application Number: 10/030,378

Filing Date: November 9, 2001

Title of the Invention: DETECTION OF VIRAL STABILITY

Examiner: Le, Emily M.

Art Unit: 1648

Appeal Number: 2007-4454

REQUEST FOR REHEARING

CERTIFICATE OF EXPRESS MAILING

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Gabriele B Crowley Gabriele B Crowley 1/4/08

Name Signature Date

Appellant requests a rehearing for the decision provided by the Board of Patent Appeals and Interferences ("the Board") in Appeal 2007-4454 on November 6, 2007. The Board's decision affirmed the Examiner's rejection of claims 1-8, 18-23 and 25. The Examiner's rejection of claim 24 was reversed and a new rejection for claim 24 was provided.

It is respectfully submitted that in affirming the Examiner's rejection the Board relied on a new and broader interpretation of the claims than previously asserted by the Examiner. The new interpretation amounts to a new rejection.

The broader interpretation is provided with respect to reference in the claims to two or more different time intervals. The Board argues two or more time intervals merely exclude performing step (a) and step (b) "simultaneously". (Board decision at page 5, first paragraph.) No citations to any Examiner arguments clearly setting forth the Board position concerning interpretation of time intervals was provided.

The breadth of the claims now advocated by the Board runs contrary to express claim descriptions and is not a "reasonable" interpretation. In addition, prior arguments presented by the Examiner do not refer to time intervals as only excluding simultaneously. Rather, as further pointed out below, the Examiner's rejection refers to discrete time intervals as zero time and days.

Appellant also respectfully point out that the Board fails to provide a specific rationale for modifying Banki (Banki *et al.* "Molecular Ordering in HIV-induced Apoptosis," *The Journal of Biological Chemistry,* Vol. 273, No. 19, pp. 11944-11953 (May 1998)), to measure the activity of a virus in different formulations. While acknowledging that Banki does not specifically look at different formulations, the Board points out that Banki looks at different cell types. (Board decision at page 13, last paragraph) The Board goes on to conclude that given Wu's (U.S. 6,689,600) teaching on the significance of formulations on structural integrity it would be obvious to the skilled artisan to look at apoptosis and caspase 3 activity of different formulations. (Board decision at page 13, last paragraph.)

The Board fails to indicate why Banki's use of different cells types would lead to a modification where the same virus is keep in different formulations and the activity of the virus in the different formulations is measured. As further discussed below, the argument presented by the Board to modify Banki based on Wu, also illustrates a teaching away from the proposed

combination in that using different formulations in Banki would cause experimental variation based on the formulation.

The arguments presented below focus on: (I) the broader claim interpretation proposed by the Board; (II) the Board's argument for modifying Banki based on Wu; (III) the new rejection to claim 24; and (IV) additional rejections and other points believed misapprehended or overlooked by the Board.

I. Interpretation of Two or More Time Intervals

Interpreting two or more time intervals between steps (a) and (b) as a discrete experimental time points allowing for difference in activity, distinguishes Banki for the reasons noted in the Applicants Appeal Brief and Reply Brief. (See Appeal Brief at pages 10-11, and Reply Brief at pages 2-3.) Briefly, Banki's describes a continuous time-course. The data for the continuous time-course was generated by initially infecting a set of cells, then at different times measuring apoptosis from the initially infected cells. Banki does not repeat both steps (a) and (b) are at two or more time intervals.

Claims 1-3 and 7 stands allegedly anticipated by Banki based on the Board interpreting claim 1 as only excluding performing step (a) and step (b) "simultaneously". The Board argues that the time interval required by Banki to start different experiments provides for taking a virus from a particular formulation at different times. (Board decision at page 5, second paragraph.)

The Board does not refer to any particular time interval required by Banki to start the different experiments. For example, the Board does not indicate whether it took more than a few seconds. Instead, the Board merely indicates that the time could not be simultaneous.

The Board indicates interpreting two or more time interval as only excluding performing step (a) and step (b) simultaneously provides the claim with the broadest reasonable interpretation. The only rationale provided by the Board for the interpretation being reasonable is that a specific time interval was not referred to in the claim. (Board decision at page 5, first paragraph.)

No consideration appears to be given to how the skilled artisan would view reference to two or more time intervals in light of claim as a whole or the prior art. Although the patent office must give claims their broadest reasonable interpretation, the interpretation must be

consistent with the one that those skilled in the art would reach. *In re Cortright*, 165 F.3d 1353, 1358, 49 USPQ2d 1464, 1467 (Fed. Cir. 1999). The interpretation provided by the Board is both a new argument and is contrary to how the skilled artisan would interpret the claims.

A. Reference in the Claims to Two or More Time Intervals

Reference in the claims to two or more time intervals provides for discrete experimental time points. The time interval is sufficient for a difference in activity to be observed. As illustrated by, for example, Figures 1 and 2 of the present application, different time points could be used. Thus, a particular time above that sufficient for there to be a difference in activity is not essential to the invention and a wide range of time intervals can be employed.

The express language of claim 1 provides for discrete experimental time intervals sufficient for there to be a difference in activity:

> 1. A method for assaying activity of a virus to **determine viral stability and potency** comprising the steps of:
>
> (a) contacting a plurality of cells susceptible to caspase 3 induction with said virus obtained from a first formulation, wherein said virus induces caspase 3 activity; and
>
> (b) measuring said caspase 3 activity as an indication of virus activity,
>
> wherein said steps (a) and (b) are repeated with either: (i) said virus taken from a second formulation, said second formulation being different than said first formulation, and the difference in caspase 3 activity from said virus taken from said first and second formulation provides an indication of virus stability and potency in said first formulation compared to said second formulation; or (ii) said virus taken from said first formulation at **two or more time intervals and the difference in caspase 3 activity between said two or more time intervals provides an indication of virus stability and potency in said first formulation**. [Emphasis added.]

The language noted in bold clearly provides for taking the virus from a particular formulation at two different time intervals as discrete experiment time intervals sufficient for there to be a difference in activity. The time it presumable took Banki to start a few different experiments by repeatedly taking a virus from a particular formulation would not be considered different discrete experimental time intervals.

B. Banki Supports Reference in the Claims to Time Intervals as Not Limited to Merely Excluding Simultaneously performing Steps (a) and (b)

Banki itself treats the time required to start the experiments as a single time point and not as different time intervals. For example, Banki provides for a single zero time in its Fig. 2, and does not indicate any variation in the zero time. (Banki at page 11946.)

Thus, assuming Banki started experiments sequentially as suggested by the Board, Banki is evidence that the skilled artisan would not interpret the difference it took to start the experiment as two or more time intervals.

C. Prior Arguments by the Patent Office Indicate an Understanding that Reference to Two or More Time Intervals are Discrete Experimental Time points and do not Merely Exclude "Simultaneously"

The arguments presented by the Examiner during prosecution of the present application do not clearly indicate an interpretation of time intervals as only excluding "simultaneously". The Examiner had ample opportunity to make an argument as provided by the Board concerning Banki providing for different times by sequentially starting different experiments. Instead of making such as argument, the Examiner refers to Banki providing different experimental time points in days.

In the Examiner Answer mailed December 28, 2006, the Examiner argues:

> . . . In addition to measuring caspase-3 activity at time zero, Banki et al. also measured caspase-3 activity at **day 2, 4, 6, and 8** – as shown in Figure 2; and at **day 2, 4, and 7** – as shown in Figure 5. Thus, not only did Banki measure caspase-3 activity at one time interval, Banki et al. also measure caspase-3 activity at **several time intervals**. [Emphasis added.]

(Examiner's Answer, last sentence of the bottom of page 11 to top of page 12.) In the next paragraph, the Examiner argues:

> Repeating steps a) and b) at two or more time intervals. See last sentence of caption provided for Figures 2 and 5, pages 11946 and 11949, respectively, of Banki et al. In the instant case, Banki et al. teaches repeating steps a) and b) with both HIV infected Jurkat-tat and H9 cells three different times in order to present the data in mean standard error form. Like above, in addition to measuring caspase-3 activity each time, at time zero, Banki et al. also measured caspase-3 activity at day **2, 4, 6, and 8** – as shown in Figure 2; and at day **2, 4, and 7** – as shown in Figure 5. **Thus not only did Banki repeat steps a) and b) numerous times, Banki et al. also measures caspase-3 activity at several different time intervals.** [Emphasis added.]

(Examiner's Answer, second bullet on page 12.) In the next paragraph the Examiner goes on to argue:

> With regard to the last bullet, Banki et al. clearly notes a repeat of the cell infection step at different times. See Figures 2 and 5, and particularly the last sentence of caption provided for the figures, pages 11946 and 11949, respectively. At the cited passage Banki et al. notes that the data shown, which is the level of caspase-3 activity, is the mean +/- S.E. (standard error) of **four experiments**. With four different experiments conducted, it is clear that a) contacting cells that are susceptible to caspase 3 induction with a virus, where the virus induces caspase 3 activity, and b) measuring said caspase 3 activity was repeated numerous time. Furthermore, it should be noted that in addition to measuring caspase 3 activity at time zero, Banki et al. also measured caspase 3 activity at day 2, 4, 6 and 8, as shown by Figure 2; and day 2, 4, and 7, as shown by Figure 5 of Banki et al. Thus, in addition to repeating the process three or more times, Banki et al also collected the data at different time intervals. Hence, contrary to Appellant's assertion, Banki et al. does clearly teaches repeating the cell infection step using HIV obtains from a first formulation at different time intervals. [Emphasis in original.]

(Examiner's Answer, bottom of page 12 to top of page 13.)

Throughout the patent office's argument, a distinction was drawn between repeating experiments and time intervals. Consistently, specific time intervals are referred to as days and treated as a discrete experimental times. The Examiner does not refer to the time it takes to start different experiment within a particular time point as different times.

II. Measuring Viral Activity in Different Formulations

The Board affirmed to the rejection of Claims 1, 20, 23 and 25 based on the combination of Banki, Wu, and Duncan (Duncan *et al.,* "Rubella Virus-Induced Apoptosis Varies among Cell Lines and Is Modulated by Bcl-X_L and Caspase Inhibitors," *Virology,* Vol. 255, pp 117-128 (199). (Board decision at page 13, last paragraph.) The Board decision refers to Banki looking at different cells types and Wu teaching the significance of formulations on biological activity. (Board decision at page 13, last paragraph and page 14, first two paragraphs.)

A. Claims 1, 20, 23 and 25

The rejection is directed to claim language concerning two different formulations. Claim 1 provides such language as follows:

> 1. A method for assaying activity of a virus to determine viral stability and potency comprising the steps of:

(a) contacting a plurality of cells susceptible to caspase 3 induction with said virus obtained from a first formulation, wherein said virus induces caspase 3 activity; and

(b) measuring said caspase 3 activity as an indication of virus activity, **wherein said steps (a) and (b) are repeated with** either: (i) **said virus taken from a second formulation, said second formulation being different than said first formulation, and the difference in caspase 3 activity from said virus taken from said first and second formulation provides an indication of virus stability and potency in said first formulation compared to said second formulation;** or (ii) said virus taken from said first formulation at two or more time intervals and the difference in caspase 3 activity between said two or more time intervals provides an indication of virus stability and potency in said first formulation. [Emphasis added.]

Claim 25 depends from claim 1 and refers to steps (a) and (b) being repeated with virus taken from a first and second formulation.

Claim 20 provides a similar description as claim 1 step (b) (i) where viral activity from two formulations are measured. Claim 20 depends from 18, where claim 18 refers to measles, mumps or rubella. Claim 23 depends from claim 20 and further describes the virus as measles or mumps. As noted in the Board decision Appellant referred to claim 23 as directed to mumps or rubella in Appellant Brief at page 16. The actual language of claim 23 provides for measles or mumps. To facilitate a review of claim 23, and the other claims in the present rejection, Appellant's arguments are focusing on use of two different formulations.

B. The Board Fails to Provide a Rationale That Would Lead a Skilled Artisan to the Proposed Modification of Banki in view of Wu

It is respectfully submitted that the Board fails indicate why Banki looking at different cell types would lead the skilled artisan to modify Banki to look at the activity of a particular virus taken from two different formulations. The Board acknowledges that Banki did not employ different formulations. (Board decision at the bottom of page 13.) Wu is cited by Board for teaching the significance of formulations on viral particles. (Board decision at the bottom of page 13.) No explanation is provided as to why Banki's use of different cells types would lead to a modification where the same virus is keep in different formulations and the activity of the virus in the different formulations is measured.

Under a recent U.S. Supreme Court decision, an obviousness inquiry is not limited to only looking to the problem the patentee was trying to solve or assuming that the skilled artisan

attempting to solve a problem would be led to prior art elements designed to solve the same problem. *KSR International Co. v. Teleflex Inc. et al.*, 127 S.Ct. 1727, 1732 (2007).

However, the Court in *KSR* also points out that to support an obviousness rejection there still needs to be articulated reasoning with some rationale underpinning.

> Following these principles may be more difficult in other cases than it is here because the claimed subject matter may involve more than the simple substitution of one known element for another or the mere application of a known technique to a piece of prior art ready for the improvement. Often, it will be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. **To facilitate review, this analysis should be made explicit.** See *In re Kahn,* 441 F.3d 977, 988 (C.A.Fed.2006) ("**[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness**"). As our precedents make clear, however, the analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ. [Emphasis added.]

Id. at 1740-1741.

The Court in *KSR* pointed to a design need or market pressure, and a finite number of predictable solutions in determining obviousness. *Id.* at 1742. In contrast, the Board does not point to specific rationales for making its proposed modification.

In addition, the fact that formulations affect viral particles teaches against modifying Banki as suggested by the Board. Banki measures HIV viral induced apoptosis. Employing different formulations would introduce experimental variations making it unclear as to whether the observed apoptosis is due to the virus or the formulation.

III. Claim 24

Claim 24 stands rejected based on Banki and Esolen (Esolen *et al.,* "Apoptosis as a Cause of Death in Measles Virus-Infected Cells, *Journal of Virology,* Vol. 69. No. 6, pp. 3955-3958 (June 1995). Banki is cited for teaching a method of measuring caspase 3 activity to quantify virally induced apoptosis. The Board indicated it would be obvious to assay caspase activity of

measles using the caspase 3 assay because Esolen specifically teaches that measles induces apoptosis. (Board decision at page 12, second paragraph.)

Claim 24 depends from claim 21 and further indicates that the virus is either measles or mumps. Claim 21 provides for measuring activity from said formulation by performing step (a) contacting cells susceptible to caspase 3 induction with a virus that induces caspase 3 activity and (b) measuring caspase 3 activity, at two or more time intervals using virus from a first formulation.

As pointed out in Argument I *supra.,* Banki fails to necessarily describe performing step (a) followed by said step (b) at two or more time intervals using virus from a first formulation. Esolen is not cited for curing the noted deficiencies in Banki.

Claim 24 further distinguishes the cited references by, for example, being directed to measuring caspase 3 activity as an indication of viral activity for either measles or mumps virus. Esolen is not concerned with determining viral activity. Esolen is directed to determining the mechanism of measles virus-induced cell death. (See Esolen abstract on page 3955.) Esolen notes that DNA fragmentation indicative of apoptosis was apparent by flow cytometry, agarose gel electrophoresis and election microscopy. (See Esolen abstract on page 3955.)

Caspase 3 while an indicator of apoptosis, provides a different read-out than DNA fragmentation. For purposes of looking at cell death described by Esolen, the Board fails to provide any evidence as to why the skilled artisan would expect apoptosis to be equivalent to looking at cell death. To support an obviousness rejection there still need to be articulated reasoning with some rationale underpinning. *KSR Intern. Co.* at 1740-1741.

The skilled artisan would not look to modify Esolen using the methods employed by Banki to determine the mechanism of measles virus-induced cell death. Esolen does not reference caspase 3 activity as involved in the observed cell death or indicate that caspase activity should be quantified. Banki measures caspase 3 activity to study HIV induced apoptosis. A prior art reference must be considered in its entirely including portions teaching away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock Inc.,* 721 F.2d 1540, 1550, 220 USPQ 303, 311 (Fed. Cir 1983), *cert. denied,* 469 U.S. 851 (1984). The Supreme Court ruling in *KSR* did not overturn *W.L. Gore & Associates, Inc. v. Garlock Inc.*

IV. Additional Rejections and Other Points Believed Misapprehend or Overlooked by the Board

A. Claims 1-3 and 7 are not Anticipated under 35 U.S.C. § 102(b) by Banki

The Board maintained the rejection of claims 1-3 and 7 as allegedly anticipated by Banki based on interpreting the time interval between steps (a) and (b) as merely excluding "simultaneous". As discussed in Argument I. *supra.*, the Board's interpretation is a new rejection and is based on an improper claim interpretation. The time it takes to start different experiments as suggested by the Board would not be considered by the skilled artisan as two or more different intervals.

In addition, reference was made in Applicant's Reply Brief to the Examiner failing to reference a particular formulation. (Reply Brief at page 2, third paragraph.) The reference was made to highlight the nature of the rejection which fails to particularly point out the exact steps used in Banki as a basis for anticipation. The Examiner's rejection generally referred to figures and required applicant to "guess" as to the exact steps presumably performed Banki.

It is respectfully submitted that the Board rejection while providing addition information, does not perform a step by step analysis to show anticipation. In addition to the points noted above in Argument I. *supra.*, the Board refers to the formulation of virus used as HIV-1 DNA clone 4803. (Board decision at page 6, third paragraph.) HIV-1 DNA clone 4803 is a particular virus, not a formulation.

The Patent Office bears the initial burden of presenting a *prima facie* case of unpatentability. *In re Oetiker* 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Anticipation requires each and every element as set forth in the claim to be described expressly or inherently in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California,* 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987), *cert. denied,* 484 U.S. 827 (1987).

B. Claims 4, 5, 18, 19, and 21 are Not Obvious Under 35 U.S.C. § 103(a) Based on Banki in View of Duncan

The Board decision upheld the obviousness rejections of claims 4, 5, 18, 19, and 21 based on Banki in view of Duncan. Duncan is cited for describing rubella virus inducing apoptosis in Vero and RK13 cells, where Duncan quantified the number of detached cells as an indicator of apoptosis. Banki is argued to provide for measuring activity from a formulation by performing step (a) followed by said step (b) at two or more time intervals. The Examiner argued that

Duncan is deficient in not teaching measurement of caspase 3 activity and that one skilled in the art would be combine Banki with Duncan to quantify viral induced apoptosis using caspase 3 activity. (Examiner's Answer at pages 6 and 7.)

Appellants Brief argued the claims as follows: (A) claims 4, 5 and 21; (B) claims 18 and 19; and (C) claim 24. The Board ruled on claims 4, 5, 18, 19 and 21 as being part of the same group, on the basis that the argument presented for these groups are essentially the same. (Board decision at page 7, footnote 1.)

Appellants respectfully disagree with the claims 4, 5 and 21 being grouped with claims 18 and 19. Claims 4, 5 and 21 ultimately depend from claim 1, which references either two different formulations (step (b)(i)), or two different time intervals (step (b)(ii)). Claims 18 and 19 do not contain steps (b)(i) or (b)(ii) from claim 1. Appellants Appeal Brief and Reply Brief both noted the dependency of claims 4, 5, and 21 on claim 1, and provided an argument based on such dependency. (Appellants Appeal Brief on page 12 and Reply Brief on page 4.)

1 Claims 4, 5, and 21

Claims 4, 5, and 21 distinguish the provided rejection, for example, by incorporating a descriptions of: (1) measuring activity from said formulation by performing step (a) contacting cells susceptible to caspase 3 induction with a virus that induces caspase 3 activity and (b) measuring caspase 3 activity, at two or more time intervals using virus from a first formulation; and (2) employing either measles, mumps or rubella.

The Board in maintaining the Examiner's rejection indicates that as caspase 3 is one of the major group of effector caspases it would have been obvious to the skilled artisan to assay caspase 3 activity of rubella using the caspase 3 assay of Banki, because Duncan specifically teaches that Rubella induces apoptosis. (Board decision at page 8, second paragraph.)

As noted above in Argument I. *supra.,* Banki fails to necessarily describe performing step (a) followed by said step (b) at two or more time intervals using virus from a first formulation. Duncan is not cited for curing the noted deficiencies in Banki.

Claims 4, 5, and 21 further distinguish Banki in view of Duncan based on the claim description concerning the virus being either measles, mumps or rubella. Duncan teaches measuring apoptosis in general by quantifying detached cells. The Board proposal to modify

Duncan to measure caspase 3 activity as indication of viral activity is inconsistent with Duncan looking for effects caused by apoptosis in general.

Appellant's argument concerning the suitability of the combination is not directed to the precise teaching or the subject matter of the claim. (Board decision at the bottom of page 8.) Rather, the argument points out that the proposed modification is not consistent with the purpose provided for in the cited reference. A prior art reference must be considered in its entirely including portions teaching away from the claimed invention. *W.L. Gore & Associates, Inc.,* 721 F.2d at 1550, 220 USPQ at 311.

Duncan is not concerned with measuring viral activity. Duncan concerns studying the cellular basis of the ability of the rubella virus to cause system birth defects in the fetuses of infected women. (See Duncan abstract, first two sentences.) Duncan indicates that other caspases, in addition to caspase 3, are involved the observed apoptosis. (Duncan at page 125, first column, third paragraph.)

Given the focus in Duncan to look at apoptosis in general, Duncan teaches away from looking at caspase 3 activity alone or in combination with other particular caspases as an indication of viral activity. Banki measures caspase 3 activity to study HIV induced apoptosis and does not indicate that such techniques are suitable for studying the cellular basis of the ability of the rubella virus to cause system birth defects in the fetuses of infected women.

2. Claims 18 and 19

Claims 18 and 19 distinguish the provided rejection, for example, by employing either measles, mumps or rubella. As noted in Argument IV.B.1 *supra.,* the Board proposal to modify Duncan to measure caspase 3 activity as indication of viral activity is inconsistent with Duncan looking for effects caused by apoptosis in general. A prior art reference must be considered in its entirely including portions teaching away from the claimed invention. *W.L. Gore & Associates, Inc.,* 721 F.2d at 1550, 220 USPQ at 311.

C. Claim 6 is Not Obvious under 35 U.S.C. § 103(a) Based on Banki in View of Wu

The Board decision upheld the obviousness rejections of claim 6 based on Banki as applied to claims 1-3, in view of Wu. Wu is cited for teaching that lyophilization improves stability of viral vaccine and recombinant proteins. (Board decision at page 12.)

Claim 6 depends from claim 1. As noted in Argument I. *supra.,* claim 1 distinguishes Banki, for example, by indicating steps (a) and (b) are repeated at two or more time intervals using a virus from a first formulation. Wu fails to cure such deficiencies in Banki.

D. Claim 8 is Not Obvious Under 35 U.S.C. § 103(a) Based on Banki in View of Goodrich

The Board decision upheld the obviousness rejections of claim 8 based on Banki as applied to claims 1-3 in view of Goodrich (U.S. Patent No. 5,958,670). Goodrich is cited for teaching a method of storing cells by freezing and later thawing. (Board decision at page 10.)

Claim 8 depends from claim 1. As noted in Argument I. s*upra.,* claim 1 distinguishes Banki, for example, by indicating steps (a) and (b) are repeated at two or more time intervals using a virus from a first formulation. Goodrich fails to cure such deficiencies in Banki.

E. Claim 22 is Not Obvious Under 35 U.S.C. § 103(a) Based on Banki in View of Esolen

The Board decision upheld the obviousness rejections of claim 22 based on Banki in view of Esolen. Banki is cited for teaching a method of measuring caspase 3 activity to quantify virally induced apoptosis. Esolen is cited for teaching that measles virus induces apoptosis. The Board indicated it would be obvious to assay caspase activity of measles using the caspase 3 assay because Esolen specifically teaches that measles induce apoptosis. (Board decision at page 12, second paragraph.)

Claim 22 distinguishes the cited references by, for example, being directed to measuring caspase 3 activity as an indication of viral activity for either measles or mumps virus. Esolen is not concerned with determining viral activity. Esolen is directed to determining the mechanism of measles virus-induced cell death. (See Esolen abstract on page 3955.) Esolen notes that DNA fragmentation indicative of apoptosis was apparent by flow cytometry, agarose gel electrophoresis and election microscopy. (See Esolen abstract on page 3955.)

Caspase 3 while an indicator of apoptosis, provides a different read-out than DNA fragmentation. For purposes of looking at cell death described by Esolen, the Board fails to provide any evidence as to why the skilled artisan would expect apoptosis to be equivalent to looking at cell death. To support an obviousness rejection there still need to be articulated reasoning with some rationale underpinning. *KSR Intern. Co.* at 1740-1741.

The skilled artisan would not look to modify Esolen using the methods employed by Banki to determine the mechanism of measles virus-induced cell death. Esolen does not reference caspase 3 activity as involved in the observed cell death or indicate that caspase activity should be quantified. Banki measures caspase 3 activity to study HIV induced apoptosis. A prior art reference must be considered in its entirely including portions teaching away from the claimed invention. *W.L. Gore & Associates, Inc.* 721 F.2d at 1550, 220 USPQ at 311.

Please charge deposit account 13-2755 for fees due in connection with this Request for Rehearing.

Respectfully submitted,

By _____

Sheldon O. Heber
Reg. No. 38,179
Attorney for Appellants

Merck & Co., Inc.
RY60-30
P.O. Box 2000
Rahway, NJ 07065-0907
(732) 594-1958